182. (Newly Added) The method of claim 141, wherein the agent comprises at least one of Lipofundin ® or Intralipid®.

183. (Newly Added) The method of claim 162, wherein the composition further comprises albumin, a growth factor(s), an attachment factor(s) or an extracellular component(s).

184. (Newly Added) The method of claim 182, wherein

the growth factor comprises at least one of keratinocyte growth factor (KGF/FGF7), epidermal growth factor (EGF) or an FGF(s);

the attachment factor comprises at least one of laminin or fibronectin; and

the extracellular matrix component comprises at least one of collagen or an heparan sulfate proteoglycan(s).

REMARKS

THE PENDING CLAIMS

Claims 108-109, 112-113, 115-130 and 132 were pending in this application and have been canceled, and claims 141-183 substituted therefor. Accordingly, claims 141-183 remain pending in this case. Reconsideration and allowance of the presently pending claims is solicited by the applicant in view of the arguments presented during the course of the interview, the newly submitted claims, and the Belkin and Fedeli declarations submitted herewith.

THE INTERVIEW

Examiner Fay is thanked for a most cordial and helpful interview granted the applicant's attorney on August 23, 2005. Prior to this date the applicant faxed to the examiner drafts of proposed new claims, an expert's declaration and clinical trial data relating to the claimed invention. During the course of the interview the applicant's attorney explained that the new claims were patentable over the previously cited prior art (the WO '91 publication), and the examiner concurred. In addition, the attorney discussed the expert declaration's establishing that a list of diseases and conditions being listed are different from "dry eye". Thereafter the discussion turned to a clinical comparison of patients treated with an agent of the invention and its comparison to a control treated with a hyaluronic acid salt. Two Declarations containing the information discussed during the interview are attached herewith. The following remarks contain the arguments exchanged at the time, and an expansion thereof.

THE OBVIOUSNESS REJECTION

Claims 108-109 and 116 stand rejected under 35USC1.103, allegedly as being unpatentable over WO 91/12808 (the WO 91 publication). This rejection is emphatically traversed.

The WO '91 publication is different from the claimed invention, and fails to describe or suggest all elements of the claimed method. As pointed out during the interview by the applicant's attorney, WO '91 is directed to a composition of phospholipids, not lipoproteins, as is the composition administered by the claimed method.

Nowhere does the WO '91 publication describe or suggest using lipoproteins, let alone for the treatment of an eye condition, as does the claimed invention. Moreover, the diseases being treated by the WO 91/12808 publication are medically different from that of the claimed method. This is clearly delineated in the Belkin Declaration submitted herewith. While the prior art relates to dry eye problems the claimed method for the treatment of disorders such as mechanical abrasion of the cornea; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical damage to the corneal epithelium and conjunctiva; chronic edema of cornea with recurrent erosion of epithelium; and conditions following damage of epithelia due to radial keratotomy. These conditions and their treatment are unrelated to the treatment of dry eyes, whether by lubrication or by suppressing inflammation. None of the therapies employed to cure the corneal conditions listed above is associated with the treatment of dry eye.

Therefore, a person skilled in the art would not consider using a dry eye medication to treat disorders listed above, except occasionally for the temporary relief of some of their minor symptoms, for the treatment of the above conditions. The Fedeli Declaration addresses the effectiveness of the claimed treatment over standard treatments employed in the art.

In view thereof, the examiner is invited to withdraw this rejection.

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Although these claims have been canceled, their contents have been incorporated into the new set of claims, and should be allowable as well.

THE AMENDMENT TO THE TITLE

The title has been amended to better correspond to the text of the present claims.

THE AMENDMENTS TO THE CLAIMS

The amendments to the claims are fully supported by the specification as filed, and by the original claims. No objectionable new matter is believed to have been introduced by the present amendments. Support for the text of claim 141 may be found as indicated in the following table showing the claim number and some of the pages that support them.

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143	6, 1-28 to 7, 1-19
144	4, 14-28; 5, 1-5; 8, 16-17
145	4, 18; 5, 4
146	2, 3; 4, 17-18
147	4, 19
148	4, 19; 2, 4-5
149	4, 22
150	4, 22
151	4, 17
152	4, 18; 2, 4
153	4, 17, 19
154	4, 20-21, 27; 5, 4, 7
155	4, 3-5
156	4, 6-10
157	4, 6-13
158	4, 8-22; 5, 10-11
159	4, 28; 5, 5
160	7, 20-21, 26-27
161	7, 26 to 8, 4; 8, 5-7
162	7, 26 to 8, 4; 8, 5-7
163	8, 9-10
164	8, 9
165	8, 10-11
166	8, 12
167	8, 12
168	8, 18-20
169	8, 23-24
170	8, 29
171	4, 15-22, 29; 5, 4; 2,8
172	
173	4, 24-25
174	6, 3-8, 9-10, 18-28; 7, 1-19
175	6, 15-17
176	6,17

177	6, 3-8
178	6, 18-20
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180	7, 7-19
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182	9, 26-27; Examples II, 1 and 2 and III
183	7, 20-21, 29; 8, 1-4
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THE TWO DECLARATIONS

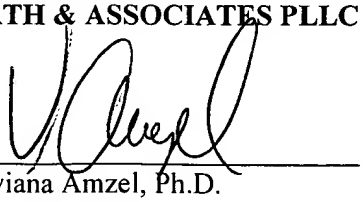
The Belkin Declaration signed by the declarant is attached for the examiner's review and consideration. As discussed during the course of the interview, the Belkin Declaration clearly establishes the difference between "dry eye" and the diseases and conditions treated by the claimed invention.

The Fedeli Declaration signed by the declarant is also attached for the examiner's review and consideration. The Fedeli Declaration describes a pilot clinical trial corresponding to the claimed process. The Fedeli Declaration shows that the claimed method of treatment is superior to the conventional Hyaluronic Acid (HA) treatment. The results of this pilot study showed a definite trend towards better efficacy for the treatment with TBX-024, the claimed treatment, than for the treatment with HA. The claimed treatment performed better, although not yet statistically significantly better, in terms of accelerating the patient's recovery time and of reducing the severity of symptomatology. Further studies are in progress to demonstrate the clinical efficacy of TBX-024 in wound healing.

Should there remain any minor issues, the examiner is requested to contact the applicant's attorney to address them.

In view of the above amendments and remarks this application is believed to be in condition of allowance. Favorable action and prompt allowance of the claims pending in this application is earnestly solicited.

Respectfully submitted,
NATH & ASSOCIATES PLLC



September 6, 2005
Date

NATH & ASSOCIATES PLLC
1030 15th Street, N.W., 6th Floor
Washington, D.C. 20005

Viviana Amzel, Ph.D.
Reg. No. 30930
Customer No.20529

IN THE UNITED STATES PATENT & TRADE MARK OFFICE

In re Appl.:	Savion N.	: Group Art Unit:	1618
Serial No.:	09/341,048	: Examiner:	Zhoreh Fay
Filed:	August 9, 1999	:	
For:	**TREATMENT OF THE EYE WITH A PHARMACEUTICAL COMPOSITION**		

AMENDMENT

Responsive to the Office Action of April 5, 2005, the period for responding being extended herewith to September 5, 2005, reconsideration and allowance of the claims is requested by the applicant in view of the following amendments and remarks.

IN THE TITLE

Please amend the title to read as follows.

-- **TREATMENT OF THE EYE WITH A PHARMACEUTICAL COMPOSITION** --.

IN THE CLAIMS

Please cancel claims 108-109, 112-113, 115-130 and 132, and substitute therefor the following claims.

Claims 108-109, 112-113, 115-130 and 132. (Canceled)

141. (Newly Added) A method of promoting healing or regeneration of damaged eye epithelium or cornea or of the anterior segment of the eye, comprising administering or applying to a subject afflicted with a disorder or condition associated with eye epithelium, cornea or anterior segment damage a therapeutic amount of an agent(s) comprising a high density lipoprotein (HDL), and/or a non-cholesterol lipid component(s) thereof able to reconstitute HDL.

142. (Newly Added) The method of claim 141, wherein the therapeutic amount of the agent(s) comprise(s) an eye epithelium regenerative amount thereof.

143. (Newly Added) The method of claim 141, wherein the agent comprises HDL, a phospholipids(s) and/or sphingolipid(s), a phospholipids(s) and at least one HDL lipid component(s) other than cholesterol and cholesteryl ester, at least one apolipoprotein(s) or a mixture thereof.

144. (Newly Added) The method of claim 141, wherein the disorder or condition comprises a corneal epithelial defect, membrane rupture, corneal damage associated with eye

surgery, eye injury associated with aging, physical, chemical, radiation or medication damage, chronic corneal edema, or pain thereof.

145. (Newly Added) The method of claim 144, wherein the eye surgery associated with corneal damage comprises laser, photorefractive keratectomy, radial keratotomy or pain thereof.

146. (Newly Added) The method of claim 144, wherein the corneal damage comprises epithelium or stroma damage, or pain thereof.

147. (Newly Added) The method of claim 144, wherein the radiation associated with eye injury comprises ultraviolet radiation or pain thereof.

148. (Newly Added) The method of claim 144, wherein the radiation associated with eye injury comprises sunlight or pain thereof.

149. (Newly Added) The method of claim 144, wherein the chronic corneal edema is associated with epithelium erosion or pain thereof.

150. (Newly Added) The method of claim 144, wherein the chronic corneal edema is associated with recurrent epithelium erosion or pain thereof.

151. (Newly Added) The method of claim 144, wherein epithelial defect comprises a spontaneous peeling of the epithelium or pain thereof.

152. (Newly Added) The method of claim 144, wherein the eye injury is associated with burns or pain thereof.

153. (Newly Added) The method of claim 141, wherein the disorder or condition comprises spontaneous peeling or a systemic disorder or condition or pain thereof.

154. (Newly Added) The method of claim 153, wherein the systemic disorder or condition comprises Sjogren syndrome, Steven-Johnson syndrome, Cicatricial pemphingoid syndrome, impaired tear film formation, those following epithelial damage associated with radial keratotomy or pain thereof.

155. (Newly Added) The method of claim 141, wherein the promotion of healing or regeneration of damaged eye epithelium comprises symptom alleviation, or curing or prevention thereof.

156. (Newly Added) The method of claim 141, wherein the eye epithelium comprises corneal and/or conjunctival epithelium.

157. (Newly Added) The method of claim 156, wherein the corneal or conjunctival epithelium comprises epithelial cells or glands.

158. (Newly Added) The method of claim 141, wherein the disorder or condition is associated with physical damage, chemical damage, a slow regeneration rate of epithelial cells, diminished conjunctival glandular secretion or pain thereof.

159. (Newly Added) The method of claim 141, wherein the disorder or condition comprises a disease or defect associated with systemic or topical medication(s) or pain thereof.

160. (Newly Added) The method of claim 141, wherein the agent further comprises albumin or an ophthalgesic agent(s).

161. (Newly Added) The method of claim 160, wherein the ophthalgesic agent(s) comprise(s) one or more of an EGF factor(s), an attachment factor(s), an extracellular matrix component(s) or an UV light protecting agent(s).

162. (Newly Added) The method of claim 161, wherein

the EGF factor(s) comprise(s) keratinocyte growth factor(s);

the attachment factor(s) comprise(s) laminin or fibronectin;

the extracellular matrix component(s) comprise(s) collagen or a heparin sulfate proteoglycan(s); and/or

the UV light protecting agent(s) comprise(s) oxybenzone.

163. (Newly Added) The method of claim 141, wherein the agent(s) is provided as a pharmaceutical composition further comprising an ophthalgesically acceptable carrier(s).

164. (Newly Added) The method of claim 162, wherein the composition is provided in the form of eye drops or a salve.

165. (Newly Added) The method of claim 162, wherein the composition comprises an emulsion, micelles or liposomes.

166. (Newly Added) The method of claim 162, wherein the composition comprises 0.1 to 20% agent(s).

167. (Newly Added) The method of claim 162, wherein the composition comprises 0.2 to 10% agent(s).

168. (Newly Added) The method of claim 162, wherein the composition comprises an hyperosmotic formulation, and may further comprise a salt(s).

169. (Newly Added) The method of claim 141, wherein at least one agent(s) is associated with a net cellular efflux of cholesterol.

170. (Newly Added) The method of claim 141, wherein the agent(s) is applied to storing and/or maintaining an isolated cornea(s).

171. (Newly Added) The method of claim 141, wherein the disorder or condition comprises at least one of mechanical abrasion of the cornea, corneal epithelial defects created by

contact lens wearing, corneal epithelial defects created by spontaneous peeling of the epithelium, corneal damage following photorefractive keratectomy, injuries caused by chemical substances, injuries caused by U.V. light exposure, corneal epithelium damage caused by medication, chronic edema of cornea with recurrent erosion of epithelium, a condition following damage of epithelia due to radial keratotomy or pain thereof.

172. (Newly Added) The method of claim 141, wherein the anterior segment of the eye comprises at least one of corneal epithelium or stromal conjunctiva.

173. (Newly Added) The method of claim 158, wherein the slow rate of regeneration is associated with at least one of old age or administration of anti-proliferative substances.

174. (Newly Added) The method of claim 141, wherein the HDL comprises at least one of human HDL, bovine HDL or reconstituted HDL comprising phospholipids and/or sphingolipids and at least one apolipoprotein.

175. (Newly Added) The method of claim 143, wherein the phospholipids comprise at least one of phosphatidyl choline, phosphatidylethanolamine, phosphatidylserine or phosphatidylinosital.

176. (Newly Added) The method of claim 143, wherein the sphingolipids comprise at least one sphingomyelin(s).

177. (Newly Added) The method of claim 141, wherein the agent comprises HDL, and at least one of a phospholipids(s), sphingolipid(s) or a lipid component(s) of HDL other than cholesterol and a cholestryl ester(s).

178. (Newly Added) The method of claim 141, wherein the non-cholesterol lipid component(s) comprises at least one of a triglyceride(s) or glycerol.

179. (Newly Added) The method of claim 141, wherein the agent further comprises at least one apolipoprotein.

180. (Newly Added) The method of claim 178, wherein the apolipoprotein(s) comprises at least one of apolipoprotein A-I, apolipoprotein II or apolipoprotein E, or apolipoprotein IV or a mixture or combination thereof.

181. (Newly Added) The method of claim 141, wherein the disorder or condition comprises at least one of dry eye, tear film disfunction caused by medication, decrease in secretion from a gland(s) located in the conjunctiva or pain thereof.

182. (Newly Added) The method of claim 141, wherein the agent comprises at least one of Lipofundin ® or Intralipid®.

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Should there remain any minor issues, the examiner is requested to contact the applicant's attorney to address them.

In view of the above amendments and remarks this application is believed to be in condition of allowance. Favorable action and prompt allowance of the claims pending in this application is earnestly solicited.

Respectfully submitted,
NATH & ASSOCIATES PLLC

September 6, 2005
Date

NATH & ASSOCIATES PLLC
1030 15th Street, N.W., 6th Floor
Washington, D.C. 20005
Tel: (202)-775-8383
Fax: (202)-775-8396

Viviana Amzel, Ph.D.
Reg. No. 30930
Customer No.20529

MAIL BOX AFTER FINAL RESPONSE
Attorney Docket 26775U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Appl. of:	Naphtali Savion	: Examiner:	Zhoreh Fay
Serial No.	09/341,048	: Group Art Unit:	1618
Filed:	August 9, 1999		

For: **TREATMENT OF THE EYE WITH A PHARMACEUTICAL COMPOSITION**

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

The undersigned, Emidio Fedeli, hereby declare and say as follows.

1. I am a citizen of Italy, residing at Ciampino (Rome).
2. I have been awarded the degree of Doctor in Chemistry by the University of Rome.
3. I am currently, and have been for 8 years the Director for Research and Development Tubilux Pharma SpA, in Pomezia, Italy.
4. I am fully conversant with the medical conditions and pharmaceutical compositions employed for that purposes included in the subject matter of U.S. Patent Application Serial No. 10/048,789.
5. The following clinical study was conducted under my supervision.

6. Clinical Study

6.1 The composition employed for this study, TBX-024, contained the following ingredients in the following amounts:

Soya oil	1.25 % (w/v)
Mean chain triglycerides (MCT)	1.25 % (w/v)
Egg phospholipids	0.30 % (w/v)
Glycerol	2.15 % (w/v)
Methyl-p-hydroxybenzoate	0.05 % (w/v)
Propyl-p-hydroxybenzoate	0.01 % (w/v)
Tocopherol	0.02 % (w/v)
Purified water	q.s. to 100ml

6.2 The primary objective of this pilot study was to evaluate the effect of a phospholipid-based microemulsion named TBX-024, which is the subject of U.S. Patent Application No. 09/341,048, on both the extent of the erosion and the recovery time.

6.3 The secondary objective was to evaluate the effect of TBX-024 on either the objective or subjective symptoms and on ocular and systemic tolerance.

7. Study Design

The study was designed as a randomized single blind clinical study, and conducted as follows:

7.1 Thirty patients suffering from non-infectious corneal erosion were included in the study.

7.2 Fifteen patients were then treated each with one drop, four times a day for five days of TBX-024 having the composition described above.

7.3 The remaining 15 patients were treated with 0.2% sodium hyaluronate (HA), which was instilled with one drop, four times a day for five days.

8. Evaluation Criteria/Efficacy Variables

For evaluation of the study, certain criteria were developed.

8.1 A primary efficacy variable was developed to measure the size of the lesion by fluorescein staining and for the complete recovery time in hours.

8.2 A secondary efficacy variable used Visual Analogic Scales (VAS) for subjective and objective symptoms.

8.3 A subjective symptom was classified either as feelings of pain, lachrymation, photophobia or foreign body sensation.

8.4 An objective symptom was classified as conjunctival hyperemia, chemosis or edema.

8.5 The last criterion used was tolerability, with a global local tolerance assessment by an investigator on a VAS and a global local tolerance assessment by the patient on a VAS. These assessments were used to asses systemic safety variables and to evaluate adverse events.

9. Results

9.1 Efficacy

The results of this study demonstrated that the patients treated with the TBX-024 had a faster recovery time and a faster reduction of the severity of both the possible objective and the subjective symptoms

when compared to the patients that received the HA treatment. Both products employed in the study were judged efficacious by an investigator and the patients.

9.2 Tolerability & Safety

With regards to tolerability and safety, both local and systemic tolerance appeared to be very good with both of the study products.

10. Conclusion

The results of this pilot study showed a trend towards better efficacy for the treatment with TBX-024, the treatment of the above-identified patent application, than for the treatment with HA. The treatment of the above-identified patent application performed better, although not yet statistically significantly, in terms of accelerating the patient's recovery time and of reducing the severity of symptomatology. Further studies are in progress to demonstrate the clinical efficacy of TBX-024 in wound healing.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

September 6, 2005

Date

Dr. Emidio Fedeli
Research and Development Director
Tubilux Pharma SpA

BEST AVAILABLE COPY

MAIL BOX FINAL RESPONSE
Attorney Docket: 26775U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Appl. of:	Naphtali Savion	: Examiner:	Zoreh Fay
Serial No.	09/341,048	: Group Art Unit:	1618
Filed:	August 9, 1999		
For:	**PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF THE EYE**		

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

The undersigned, Michael Belkin, hereby declare and say the following.

1. I am a citizen of Israel, residing in Tel Aviv, Israel.

2 I am a Professor of Ophthalmology at the Tel Aviv University and the Director of Ophthalmic Technologies Laboratory at the University's Eye Research Institute at the Sheba Medical Center. I was awarded a Master's degree in Science by Cambridge University, in England, and a Medical Doctoral degree from the University of Jerusalem, in Israel.

3. I have previously served as Director of Research, Development and Non-Conventional Warfare Medicine in the Israel Defense Forces Medical Corps, Director of the Tel Aviv University Eye Research Institute and Chairman of the Tel Aviv University Department of Ophthalmology, and President of the Israel Society of Eye and Vision Research as well as one of the founders.

4. I am the author of over 200 scientific publications and of 15 patents. I am an internationally recognized eye researcher and have received various research awards. My laboratory is dedicated to enabling the transfer of technologies from the university-level research to clinical practice by providing expertise and facilities for the laboratory, pre-clinical and the clinical studies.

5. I am currently involved in several projects in lasers, optics, ophthalmic devices, pharmaceutics and biotechnology, all of which are at various stages of development. I have been investigating the process of corneal healing for many years and, given that my laboratory is dedicated to the transfer of technologies from the laboratory to the clinic, I am well cognizant of both the research and the clinical practice on the subject.

6. I am fully conversant with the medical conditions and pharmaceutical compositions incorporating a binder, including the subject of U.S. Patent Application Serial No. 10/048,789.

7. I wish to provide my professional opinion in support of the following statement made by the inventors that a medicament for the treatment of disorders selected from the group consisting of: mechanical abrasion of the cornea; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical damage to the corneal epithelium and conjunctiva; chronic edema of cornea with recurrent erosion of epithelium; and conditions following damage of epithelia due to radial keratotomy, i.e., the subject of the above-identified patent application, is unrelated to the treatment of dry eyes, whether by lubrication or inflammation suppression.

8. Furthermore, none of the therapies employed to cure the corneal conditions listed above is associated with dry eyes treatment.

9. Consequently, a person skilled in the art would not consider using a dry eye medication to treat disorders listed above, except occasionally for the temporary relief of some of their minor symptoms, for the treatment of the above conditions.

10. The undersigned Declarant declares further that all statements made herein of their own knowledge are true ad that all statements made on information and belief are believed to be true; further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon..

September 5, 2005

Date

פרופ' מיכאל בלקין
רופא עיניים
מס. רשיון 8339

Michael Belkin, M.A., M.D.
Director, Ophthalmic Technologies Laboratory
Eye Research Institute, Sheba Medical Center
Tel Aviv University